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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/505,788	02/17/00	OLSON R	PH-7076-A

HM12/0125

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EXAMINER	
COLEMAN, B	
ART UNIT	**PAPER NUMBER**
1624	4

DATE MAILED: 01/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/505,788	OLSON
Examiner	**Group Art Unit**
Brenda Coleman	1624

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) *7, 9, 17, 19, and 21* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6, 8, 10-16, 18, 20, and 22-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-24 are pending in the application.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, 7, 10, 12-15, 17, 20 and 22-24, drawn to compounds, compositions and method of use of the compounds of formula I, where B forms a benzoazepine ring, classified in class 514, subclass 212.07 and class 540, subclass 523.

II. Claims 1-6, 8, 10-16, 18, 20 and 22-24, drawn to compounds, compositions and method of use of the compounds of formula I, where B forms a benzodiazepine ring, classified in class 514, subclass 221 and class 540, subclasses 504, 505, 506, 509, 517 and 518.

III. Claims 1-5, 12-15 and 22-24, drawn to compounds, compositions and method of use of the compounds of formula I, where B forms an azepine ring, classified in class 514, subclasses 212.03 and 212.08 and class 540, subclasses 524, 525, 526 and 527.

IV. Claims 1-5, 9-15, 19, 20 and 22-24, drawn to compounds, compositions and method of use of the compounds of formula I, where B forms a dibenzoazepine ring, classified in class 514, subclass 212.04 and class 540, subclass 522.

V. Claims 1-3, 12, 13 and 22-24, drawn to compounds, compositions and method of use of the compounds of formula I, where B forms a ring not embraced by Groups

I-IV above, classified in class 514, various subclasses within and class 540, various subclasses within.

VI. Claim 21, drawn to the method of use of the compounds of formula I, classified in class 514, various subclasses within and class 540, various subclasses within.

The inventions are distinct, each from the other because of the following reasons:

Groups I-VI are directed to structurally dissimilar compounds such that the variable core created by the varying definition of B in formula I do not belong to a recognized class of chemical compounds in the art, and references anticipating one invention, would not render obvious the others, for example azepine is different from benzodiazepine, dibenzoazepine, etc. Thus, separate searches in the literature as well as in the U.S. Patent Classification System would be required. Each group's compounds are made and used independently of each other and could support separate patents. The compounds differ significantly in chemical structures. One skilled in the art would not consider such diverse structures as functional equivalents of each other. The mere fact that there is a single similarity is not in itself a significant reason to render the whole embodiment obvious.

During a telephone conversation with Scott Larsen on January 18, 2001 a provisional election was made with traverse to prosecute the invention of Group II, claims 1-6, 8, 10-16, 18, 20 and 22-24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 7, 9, 17, 19 and 21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

1. Any non-provisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Cross - references to other related applications may be made when appropriate.

"This application is a continuation-in-part of application Serial Number 09/469,939, filed December 24, 1999, which claims the benefit of U.S. Provisional Application No. 60/113,588, filed December 24, 1998." is suggested.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information

submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

3. The disclosure is objected to because of the following informalities: the text of page 2 is smeared.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 8, 10, 12-16, 18, 20 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-6, 8, 10, 12-16, 18, 20 and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1 and 22-24 are vague and indefinite in that it is not known what is meant by "at each occurrence" since there is only one R^1 variable.

b) Claims 1 and 22-24 are vague and indefinite in that it is not known what is meant by "C_1-C_6 alkyl Cl," in the definition of R^{1a}.

c) Claims 1-6, 8, 10, 12-16, 18, 20 and 22-24 are vague and indefinite in that the list of substituents for the variables R^{1b}, R^{4b}, R^{5c}, R^{6b}, R^{10b}, R^{11}, R^{11b}, R^{12a}, R^{12b} and R^{17a} includes trifluoroalkyl which is embraced by haloalkyl, and thus results in double inclusion. See Ex parte White 127 USPQ 261.

d) Claims 1, 2, 12 and 22-24 are vague and indefinite in that it is not known what is meant by C_1-C_4 halothioalkyl-S- in the definitions for the variables R^{4b}, R^{5c}, R^{11b}, R^{12a} and R^{12b}.

e) Claim 4 is vague and indefinite in that the variable R^{19} appears to be the last definition, however, variable R^{18} is not followed by an "and" to indicate the end of the claim.

f) Claims 5, 6, 8, 10, 15, 16, 18 and 20 recite the limitation "**3** R^{13}'s" in the structural formulae of ring B. There is insufficient antecedent basis for this limitation in the claim.

g) Claims 10 and 20 are vague and indefinite in that the definition of R^3 includes a moiety which has a carbon atom containing five bonds, i.e. $-CH_2(CH_3)_2$. See line 27 on page 210 and line 7 on page 246.

h) Claims 10 and 20 recite the limitation "$-CH_2C(CH_3)_3$" in the definition of R^3. There is insufficient antecedent basis for this limitation in the claim. The maximum number of carbon atoms in the claims from which this claim depends is 4.

i) Claims 10 and 20 recite the limitation "$-CF_3$" in the definition of R^3. There is insufficient antecedent basis for this limitation in the claim. The maximum number of R^{4a} substituents on the carbon atoms in the claims from which this claim depends is 1.

j) Claims 10 and 20 recite the limitation "$-CH_2CH=C(CH_3)_2$, $-CH_2CH_2C(CH_3)=CH_2$, $-CH_2CH_2CH=C(CH_3)_2$, cis-$CH_2CH_2CH=CH(CH_3)$, trans-$CH_2CH_2CH=CH(CH_3)$," in the definition of R^3. There is insufficient antecedent basis for this limitation in the claim. The maximum number of carbon atoms in the claims from which this claim depends is 4.

k) Claims 10 and 20 recite the limitation "$-CF_3$" in the definition of R^5. There is insufficient antecedent basis for this limitation in the claim. The maximum number

of R^{5b} substituents on the carbon atoms in the claims from which this claim depends is 1.

l) Claims 10 and 20 recite the limitation "-$CH_2CH_2CH_2C{\equiv}CH$, -$CH_2CH_2CH_2C{\equiv}C(CH_3)$, -$CH_2CH_2CH_2C{\equiv}C(C_6H_5)$" in the definition of R^5. There is insufficient antecedent basis for this limitation in the claim. The maximum number of carbon atoms in the claims from which this claim depends is 4.

m) Claims 10 and 20 are vague and indefinite in that there is a definition for the variable R^{10}, however, there is no variable R^{10} in the claims from which these claims depend.

n) Claims 10 and 20 are vague and indefinite in that there is a definition for the variable R^{11}, however, there is no variable R^{11} in the claims from which these claims depend.

o) Claim 12 is vague and indefinite in that the variable R^{10a} appears to be the last definition, however, variable R^{10} is not followed by an "and" to indicate the end of the claim.

p) Claim 14 is vague and indefinite in that the proviso at the end of the claim is narrower than the claim from which it depends. Clarification is requested.

q) Claim 16 is vague and indefinite in that a period appears at the end of line 11 on page 235 indicating the end of the claim which is not so.

r) Claim 18 is vague and indefinite in that a period appears at the end of line 31 on page 242 indicating the end of the claim which is not so.

s) Claim 20 recites the limitation "1-benzimidazolyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

t) Claim 20 recites the limitation "morpholino" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

u) Claim 20 is vague and indefinite in that it is not known what is meant by "N-piperinyl".

v) Claim 20 recites the limitation "(1-benzimidazolyl)CH_2-" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

w) Claim 20 recites the limitation "(morpholino)CH_2-" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

x) Claim 20 is vague and indefinite in that it is not known what is meant by "(N-pipridinyl)CH_2-".

y) Claim 20 recites the limitation "(1-benzimidazolyl)CH_2CH_2-" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

z) Claim 20 recites the limitation "(morpholino)CH_2CH_2-" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

aa) Claims 23 and 24 are vague and indefinite in that the claims provide for the use of the claimed compounds, but the claims do not set forth any steps involved in

determining which are the diseases capable of being mediated by inhibiting γ-secretase activity and β-amyloid production. It is unclear which diseases are mediated by inhibiting the activity of γ-secretase and β-amyloid production? Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of

administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in neurologics, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific

disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6, 10-16, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graham et al., U.S. Patent No. 5,998,407. The generic structure of U.S. '407 encompasses the instantly claimed compounds (see Formula I, column 3) as claimed herein. Examples 1-10

differ only in the nature of the R^a substituent. Column 3, line 35 through column 6, line 6 defines the substituent R^a as $V(R^8)_r$-$A^1(CR^{1a}{}_2)_n A^2(CR^{1a}{}_2)_n$-$(Z(R^9))_u$-$(CR^{1b}{}_2)_p$-X-,. where X is -C(=O)-, (p is 0-2 and n is 0-2, where the sum of p and n is 2), u is 0, A^2 is -C(O)-, the n between A^2 and A^1 is 0, A^1 is $-N(R^{10})-$, V is hydrogen, heterocycle, aryl, C_1-C_{20} alkyl. Compounds of the instant invention are generically embraced by U.S. '407 in view of the interchange ability of the R^a substituent of the benzodiazepine ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example 2-(2-methylpropyl)-3-allyl-butanediamide as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 5, 6, 8, 10-16, 18 and 20 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 5, 6, 8, 10-16, 18 and 20 of copending Application

No. 09/469,939. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-4 and 22-24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 22-24 of copending Application No. 09/469,939. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of U.S. '939 embrace the compounds of formula (I) when B is benzodiazepine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Monday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
January 24, 2001